REMARKS

Claims 1-5, 7, 9-11, 21-23 and 84 were pending in the present application.

Applicants have canceled claims 3 and 10, without prejudice, and amended claims 1 and 9, without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more continuing applications.

Claim 1 has been amended to clarify that which Applicants regard as the invention. Specifically, claim 1 has been amended to recite that the heterologous adenoviral E4 region or portion thereof is inserted into the replication-defective adenovirus under the control of the native E4 promoter. Support for this amendment can be found in the specification, as published as U.S. Patent Application No. 2004/0106194, for example, at paragraphs [0016], [0054] and [0056]. Claim 9 has been amended to be dependent upon claim 1.

No new matter has been added by these amendments.

After entry of the foregoing amendments, claims 1, 2, 4, 5, 7, 9, 11, 21-23 and 84 will be pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Claim Rejections – 35 U.S.C. § 112

Claim 9 was rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that there is insufficient antecedent basis for the limitation "replication-defective adenovirus" in claim 7.

Without admitting to the propriety of the rejection and in an effort to advance prosecution of the present application, Applicants have amended claim 9 to depend from claim 1. Accordingly, the rejection has been rendered moot.

Claim Rejections – 35 U.S.C. § 103

Claims 1-5, 7, 9-11, 21 and 84 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Falck-Pedersen (U.S. Patent No. 5,849,561), Mehtali (U.S. Patent No. 6,475,480), and Fallaux (Fallaux et al., 1998, Human Gene Therapy 9:1909-1917) in further view of Wickham (U.S. Patent No. 5,712,136). Applicants respectfully traverse.

The legal standard, Falck-Pedersen and Mehtali have previously been discussed in the Amendment and Response to Office Action filed on March 6, 2007 ("March 2007 Amendment").

Falck-Pedersen discloses a method of producing a replication-deficient adenovirus in which the virus is deficient in both E1 and E4 functions in a cell that provides in *trans* gene functions of the E1 and E4 regions of one or more adenoviruses not belonging to the same serogroup as the replication-deficient adenovirus. See Falck-Pedersen, abstract. Falck-Pedersen discloses that the essential gene functions of the E4 region are harmful to the host cell and so it would be useful to use a regulable promoter so that the gene function of the E4 region can be provided only when the replication deficient adenovirus is in need of the toxic gene products for its replication. See Falck-Pedersen, col. 9, lines 51-56. Falck-Pedersen does not teach the placement of the E4 ORF6 into the replication-deficient adenovirus.

Mehtali describes the "use of a polynucleotide encoding one or more ORF(s) of the E4 region of an adenovirus selected from ORF1, ORF2, ORF3, ORF4, ORF3/4, ORF6/7, ORF6 and ORF7 taken individually or in combination, to improve the expression and/or persistence of expression of a gene of interest ..." See Mehtali, abstract. Mehtali further describes that it is possible to insert certain E4 ORFs from the same or other adenovirus backbones in an adenovirus vector. See id., col. 4, lines 35-38. Mehtali discloses that the adenoviral vector may be propagated in a complementation cell line, which supplies in *trans* the deleted/mutated viral functions. See id., col. 10, lines 5-7. Mehtali further describes that it is possible to test the effect of an E4 ORF by providing it in *cis* or *trans* to a E4 deleted vector carrying a transgene and determining its expression". See id., col. 3, lines 61-64.

Fallaux provides the Ad5 E1-complementing cell line, PER.

Wickham teaches that adenovirus subgroup D comprises serotypes 24, 26 and 36.

The Examiner contends that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because (1) one would have been motivated by the teachings of Falck-Pedersen of the need for replication-deficient adenovirus of multiple strains and the ability to propagate such adenovirus in cells (such as PER cells taught by Fallaux) already known to express Ad5 E1 gene products; and (2)

there would have been a reasonable expectation of success given the above teachings of successful methods and products.

The present invention, as reflected in the amended claims, is directed, *inter alia*, to methods for propagating a replication-defective adenovirus of subgroup D, containing all or a portion of a heterologous nucleic acid sequence encoding adenoviral E4 open reading frame 6 (ORF6) from a subgroup C adenovirus in place of the native nucleic acid sequence encoding ORF6 or the complete adenoviral E4 encoding region such that the heterologous nucleic acid sequence is under the control of the native E4 promoter, in an adenoviral E1-complementing cell line expressing an E1 gene product which is not of the same serotype as the replication-defective adenovirus and where the heterologous E4 ORF6 and E1 gene products are from the same serotype. The present invention requires that expression of the heterologous nucleic acid is under the control of the native E4 promoter.

In response to Applicants' arguments of April 30, 2008 regarding Lusky teaching away from the present invention, the Examiner argues that Applicants' argument was not entirely correct, in part, because methods of regulating the toxic effects of the E4 gene products were known. Applicants note that the present invention, as reflected in the amended claims, requires the native E4 promoter. Falck-Pedersen teaches that the essential gene functions of the E4 region are harmful to the host cell and therefore, it is useful to use a regulable promoter to minimize the cell's exposure to the toxic gene products. See Falck-Pedersen, col. 9, lines 51-55. Thus, in view of the known toxicity of the E4 gene products, the person of ordinary skill in the art would have been directed to using a regulable promoter and not to retain the native E4 promoter.

Thus, Applicants respectfully submit that the prior art, as a whole, and particularly, Falck-Pedersen, teaches away from the present invention.

Claims 1 and 21-23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Falck-Pedersen, Mehtali, Fallaux and Megede (Megede *et al.*, 2000, J. Virol. 74:2628-2635). Applicants respectfully traverse.

Falck-Pedersen, Mehtali, and Fallaux have been discussed above. Megede teaches that gag is an important target for host cell-mediated immune control of HIV. See Megede, abstract.

The Examiner contends that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because (1) one would have been motivated to use HIV-1 gag as the gene of interest in order to express gag proteins for vaccines; and (2) there would have been a reasonable expectation of success given that the HIV-1 gag gene has been characterized and the underlying techniques are demonstrated to be successful.

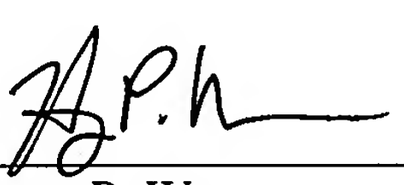
As Megede fails to remedy the deficiencies of Mehtali, Falck-Pedersen and Fallaux, with respect to independent claim 1, Applicants respectfully submit that the present invention is not obvious in view of Mehtali, Falck-Pedersen and Fallaux in view of Megede.

For the above reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. 103.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

Date: January 20, 2009 By: 

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